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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/718,998	LANDOLFI ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

DETAILED ACTION

Election/Restrictions

1. The response to the restriction requirement filed March 7, 2003 (Paper No. 7) is acknowledged. The supplemental amendment filed 7/24/2003 is acknowledged. Upon reconsideration the restriction requirement is withdrawn.

2. Claims 108-209 are pending and examined on the merits.

Specification

3. The specification is objected to. A substitute specification is required, because the application as filed is a compilation of several different applications. For example, the specification contains four different sections entitle "Background of Invention" and several sections entitled "Summary of Invention". In addition, some pages have an inadequate top margin, causing some of the text to be missing by hole punches at the top of the page. Applicant must state that the substitute specification contains no new matter. Such a statement must be a verified statement if made by a person not registered to practice before the Office. Additionally, if there are any changes made to the specification, the drawings and descriptions of the drawings much be changed to reflect these changes. Additionally, if there are changes to the text of the specification, applicant is required to point to the places in the originally filed disclosure that provide support for these changes.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically, the specification contains disclosures of sequences (in the text of the Disclosure and in the figures) that are not identified by sequence identifier.

Applicant is given the time period of this office action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

5. Claims 108-111, 113-115, 119-124, 133-169, 208 and 209 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 108, 110 and 119 contain the phrase "the amino acid", which lacks antecedent basis in the claims.

Claim 133 contains the phrase "said position" followed by a Markush group, where the phrase "said position" may either be referring to any of the three categories of positions, or just to category "III". Because it is unclear, the scope of the claim is unclear.

6. Claims 109, 111, 117, 120, 128, and 131 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 109, 111, 117, 120, 128, 131, 135, 172, 191, are 201 are drawn to humanized immunoglobulins that bind to antigen with an affinity constant of at least 10^8 M^{-1}. Thus, the claims are drawn to humanized immunoglobulins having a range of affinities where the highest affinity may be that of an antibody having an affinity constant of at least 10^8 M^{-1} (the lower the affinity constant, the higher the affinity; and because the units of affinity are a fraction, the higher the exponent the lower is the value of the affinity constant). The specification does not appear to support the claimed genus of humanized immunoglobulins. The specification teaches ranges of affinities where the lowest affinity (not the highest as set forth in the claims) is 10^8 M^{-1}, and contemplates preferred embodiments where the affinity is 10^9 M^{-1} to 10^{10} M^{-1} (which is outside the range of the affinity of the claimed immunoglobulins).

This rejection would be obviated by removing the word "constant" from the claims.

7. Claims 108-135, 137-172, 174-191, 193-201, 203-209 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized immunogloublins having affinities within 2- to 4-fold the affinity of the parent antibody, does not reasonably provide enablement for any humanized immunoglobulin having affinities much higher than that of the parent immunoglobulin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claims may be interpreted as reading on any humanized immunoglobulin with any affinity, and therefore, reads on humanized immunoglobulins that have affinities much greater than the parent immunoglobulin molecule. The specification confines its teachings to methods for making humanized immunoglobulins that have affinities that are close to the affinities of the parent immunoglobulin molecule. The specification sets forth methods to solve a problem in the art whereby binding affinity was lost by the process of CDR grafting into a human framework, by substituting amino acids in the framework, where the amino acids are ones in the framework that affect antigen binding by the CDR regions. The specification states that these methods are to be used to restore the original binding affinity of the parent molecule that is lost during CDR

grafting. The specification does not set forth methods to improve antigen binding affinity over that of the parent molecule. In fact the binding affinities of the exemplified humanized immunoglobulins only approximate that of the parent molecules, and in some instances are as much as 2-fold lower than that of the parent molecules. Thus, the specification fails to teach one of skill in the art how to make humanized immunoglobulins with any binding affinity, but only a binding affinity that approximates that of the parent molecule.

In light of the teachings of the specification and the working examples, one of skill in the art would not have a reasonable expectation of success in making the full scope of the claimed immunglobulins, because the full scope of the claims reads on immunoglobulins having much higher binding affinity than that of the parent immunoglobulin.

8. Claims 133, 138, 142, 148, 150, 158-162, 164, 166-168, 170, 175, 177, and 199 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the amendment introduces new matter into the specification as originally filed.

The claimed inventions are drawn to immunoglobulins comprising framework substitutions at positions that do not appear to have been contemplated in the specification as originally filed. Furthermore, some of the "framework" substitutions appear to have been made in regions that are designated as CDR regions by the specification. Examples of these are H66 and H103. Applicants' remarks concerning support for the claim amendments are

acknowledged, but applicants have failed to describe specifically which positions are originally numbered by the sequential method and which are originally numbered by the Kabat method. Therefore, if a specific residue recited in a claim does not appear to be taught in the specification, then such a claim is rejected for containing new matter.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 108-132 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18, 20 and 21 of U.S. Patent 6,180,370 (for claims 108-115 of instant application); claims 10, 13, 17-21, 28-30 of U.S. Patent 6,180,370 (for claims 116-124 of instant application); and claims 1, 2, 3, 5, and 25-27 of U.S. Patent 6,180,370 (for claims 125-132 of instant application). Although the conflicting claims are not identical, they are not patentably distinct from each other.

In the case of claims 108-115 of the instant application, these claims encompass the subject matter of claim 18 of U.S. Patent 6,180,370 to the extent that claim 18 depends from claim 10 or 13 of U.S. Patent 6,180,370.

In the case of claims 116-124 of the instant application, these claims encompass subject matter of claims 10, 13, 17-21, and 28-30 of U.S. Patent 6,180,370, because these claims are drawn to humanized immunogloblulins that comprise a substitution of an acceptor framework amino acid that is rare with a donor amino acid that is the same as an amino acid that is typical for that position for human immunoglobulin sequences, or comprise a framework that has either at least 65% or at least 70% identity to a donor framework. Thus, the claims read on humanized immunoglobulins that comprise variable region framework that is a consensus sequence of many human immunoglobulins, because the scope of immunoglobulins comprising a consensus framework appears to encompass these immunoglobulins.

In the case of claims 125-132 of the instant application, these claims encompass subject mater of claims 1-3, 5 and 25-27 of U.S. Patent 6,180,370, because these claims are drawn to methods of making humanized immunoglobulins that comprise a substitution of an acceptor framework amino acid that is rare with a donor amino acid that is the same as an amino acid that is typical for that position for human immunoglobulin sequences, or comprise a framework that has either at least 65% or at least 70% identity to a donor framework.

10. Claims 108-124 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, and 9-11 of U.S. Patent 5,530,101.

Although the conflicting claims are not identical, they are not patentably distinct from each other.

In the case of claims 108-115 of the instant application, these claims encompass the subgenus of humanized immunoglobulins claimed in claims 1-6, and 9-11 of U.S. Patent 5,530,101, because it appears that the preferred embodiments comprise at least 3 amino acids substituted into the human framework.

In the case of claims 116-124 of the instant application, these claims encompass the subgenus of humanized immunoglobulins claimed in claims 1-6 and 9-11 of U.S. Patent 5,530,101, because the framework regions are 65%-95% identical to a donor framework. Thus, the claims read on humanized immunoglobulins that comprise variable region frameworks that are consensus suequences of many human immunoglobulins.

11. Claims 108-132 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 7-20 of U.S. Patent 5,693,762. Although the conflicting claims are not identical, they are not patentably distinct from each other.

In the case of claims 108-115 of the instant application, these claims encompass the subject matter of claim 1-4, 7-12 and 20 of U.S. Patent 5,693,762, because these claims appear to encompass antibodies that comprise at least 3 amino acid substitutions into the framework.

In the case of claims 116-124 of the instant application, these claims encompass subject matter of claims 1-4, 7-12 and 20 of U.S. Patent 5,693,762, because these claims are drawn to humanized immunogloblulins that comprise a substitution of an acceptor framework amino acid

that is rare with a donor amino acid that is the same as an amino acid that is typical for that position for human immunoglobulin sequences, or comprise a framework that has either at least 65% or at least 70% identity to a donor framework, or comprise a framework that is a consensus sequence.

In the case of claims 125-132 of the instant application, these claims encompass subject mater of claims 13-19 of U.S. Patent 5,693,762, because these claims are drawn to methods of making humanized immunoglobulins comprise a framework that has either at least 65% identity to a donor framework, and therefore reads on making humanized antibodies comprising a consensus sequence framework.

12. Claims 108-124 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent 5,585,089. Although the conflicting claims are not identical, they are not patentably distinct from each other.

In the case of claims 108-115 of the instant application, these claims encompass the subject matter of claims 1-11. In the case of claims 116-124, these claims encompass the subject matter of claims 4, 7, 8 and 11, because these claims read on antibodies that comprise a substitution of an acceptor framework amino acid that is rare with a donor amino acid that is the same as an amino acid that is typical for that position for human immunoglobulin sequences. Thus, these claims read on immunoglobulins comprising a consensus sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 116, 119, 122, and 123 are rejected under 35 U.S.C. 102(a) as being anticipated by Riechmann (Riechmann, L. et al., Nature, 332: 323-327, 1988, March).

Claims 116, 119, 122 and 123 are drawn to humanized immunobloublins comprising a complementarity determining region (CDR) from a donor immunoglobulin and an acceptor immunoglobulin variable region framework, which humanized immunogloulin specifically binds an antigen, wherein the acceptor immunoglobulin variable region framework is a consensus framework from many human antibodies. The scope of the term "consensus framework from many human antibodies" is interpreted broadly, absent a specific definition in the specification, and because the claims do not contain complete structural detail of the framework. The scope of the term is interpreted to read on frameworks that contain at least one substitution that is made on the basis of exchanging a rare amino acid for a more typical amino acid for that particular position, or is interpreted to read on frameworks that are a combination of at least 2 antibodies.

Riechmann teaches making a humanized anti-CAMPATH-1 antibody, by grafting hypervariable regions of a rat anti-CAMPATH-1 antibody into both the human NEW and human

REI frameworks (that appears to be a consensus framework, because the legend to Figure 1 indicates that the light chain was "based on" human REI; see page 324, "Methods"), and further substituting Serine 27 with Phenylalanine and Serine 30 with Phenylalanine. Thus, Riechmann teaches antibodies that are the same as that claimed.

14. Claims 116-132 are rejected under 35 U.S.C. 102(e) as being anticipated by Huston (U.S. Patent 5,476,786; issued Dec. 19, 1995; effective filing date May 21, 1987).

Claims 116-124 are drawn to humanized immunogloublins, and pharmaceutical compositions thereof, comprising a complementarity determining region (CDR) from a donor immunoglobulin and an acceptor immunoglobulin variable region framework, which humanized immunoglobulin specifically binds an antigen, wherein the acceptor immunoglobulin variable region framework is a consensus framework from many human antibodies. The scope of the term "consensus framework from many human antibodies" is interpreted broadly, absent a specific definition in the specification, and because the claims do not contain complete structural detail of the framework. The scope of the term is interpreted to read on frameworks that contain at least one substitution that is made on the basis of exchanging a rare amino acid for a more typical amino acid for that particular position, or is interpreted to read on frameworks that are a combination of at least 2 antibodies. The claims also include humanized immunoglobulins with affinities of at least 10^8M^{-1}, immunoglobulins that are an antibody tetramer, Fab, or (Fab')2. Clams 125-132 are drawn to methods of making humanized immunoglobulins comprising selecting an acceptor heavy chain variable region framework whose sequence is a consensus sequence of human heavy chain variable region framework sequences.

Huston teaches humanized immunoglobulins that comprise "consensus sequences", and methods of making such humanized immunoglobulins, because Huston teaches humanized immunoglobulins that comprise frameworks that are homologous with a portion of the frameworks of a human immunoglobulin (see col. 2, line 60 – col. 3, line 40). Huston teaches the general concept of replacing an amino acid in a framework region of an acceptor immunoglobulin with an amino acid from a donor immunoglobulin for the purpose of increasing binding specificity of the immunoglobulin (see col. 13, lines 47-57; see col. 7, lines 40-54), and a specific working example (although not in a "humanized" immunoglobulin, see col. 13, lines 16-38). Huston teaches methods of making and purifying immunoglobulins, and assessing binding affinity (col. 14, line 50 – col. 18, line 42). Huston teaches pharmaceutical compositions (col. 7, line 62 – col. 8, line 5). Huston teaches making a Fab for the purpose of making an Fv fragment (see col. 4, line 59 - col. 5, line 3).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
December 15, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

JASEMINE C. CHAMBERS
DIRECTOR
TECHNOLOGY CENTER 1600

Notic to Comply With S quence Rules	Application No.	Applicant(s)	
	09/718,998	LANDOLFI ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

X 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 8230, May 1, 1990.

X 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

X 3. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has not been submitted as required by 37 C.F.R. 1.821(e).

___ 4. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has been submitted. However, the content of the CRF does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

___ 5. The Computer Readable Form (CRF) that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute CRF must be submitted as required by 37 C.F.R. 1.825(d).

___ 6. The paper copy of the "Sequence Listing" is not the same as the Computer Readable Form (CRF) of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

___ 7. Other: _____

Applicant Must Provide:

X An initial or substitute copy of the **CRF** "Sequence Listing".

X An initial or substitute **paper copy** of the "Sequence Listing", as well as an amendment directing its entry into the specification.

X A statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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